Claims

1. Process for changing the expression of a nucleic acid sequence which is present endogenously in a eukaryotic cell,
wherein
(a) the cell is transfected with a first vector comprising
(i) at least one sequence selected from a first heterologous expression control sequence and a first amplification gene,
(ii) a positive selection marker gene,
(iii) at least two target sequences for a site-specific recombinase flanking the sequences (i) and (ii),
(iv) DNA sequences which flank the sequences (i), (ii) and (iii) and are homologous to a nucleic acid section in the genome of the cell in order to allow a homologous recombination
(b) the transfected cell is cultured under conditions under which a homologous recombination of the vector takes place and
(c) the cell obtained according to step (b) is isolated.

2. Process as claimed in claim 1,
wherein
loxP sequences are used as recombinase target sequences.

3. Process as claimed in ~~one of the previous claims~~ Claim 2, **wherein**
the vector additionally contains a negative selection marker gene which is arranged outside the homologous sequences according to claim 1(a) (iv).

4. Process as claimed in ~~one of the previous claims~~ Claim 1, **wherein**
the nucleic acid sequence that is located between the recombinase target sequences is cut out of the genome of the cell by transient activation of a site-specific recombinase that recognizes the target sequences.

5. Vector for homologous recombination comprising,
(i) at least one sequence selected from an expression control sequence and an amplification gene,
(ii) a positive selection marker gene,
(iii) at least two target sequences for a site-specific recombinase which flank the sequences (i) and (ii),
(iv) DNA sequences flanking the sequences (i), (ii) and (iii) which are homologous to a nucleic acid section in the genome of a cell in order to allow a homologous recombination and
(v) optionally a negative selection marker gene.

6. Vector comprising
(i) at least one sequence selected from a heterologous expression control sequence and an amplification gene,
(ii) a positive selection marker gene,
(iii) at least two recombinase target sequences which

flank the sequences (i) and (ii),

(iv) optionally a negative selection marker gene.

7. Eukaryotic cell, preferably a human cell,
wherein
it
(a) contains at least one chromosomally located sequence selected from a heterologous expression control sequence and an amplification gene in operative linkage with a nucleic acid sequence that is present endogenously and
(b) this sequence is flanked by recombinase target sequences.

8. Process for changing the expression of a nucleic acid sequence that is present endogenously in a eukaryotic cell,
wherein
(a) the cell is transfected with a vector comprising
    (i) at least one nucleic acid sequence that binds an activator protein,
    (ii) a positive selection marker gene,
    (iii) DNA sequences flanking the sequences (i) and (ii) which are homologous to a nucleic acid section in the genome of the cell in order to allow a homologous recombination,
(b) the transfected cell is cultured under conditions under which a homologous recombination of the vector takes place and
(c) the cell obtained according to step (b) is isolated.

9. Process as claimed in claim 8,
wherein
at least one hypoxia-inducible factor (HIF)-binding nucleic acid sequence is used.

10. Vector for homologous recombination, comprising
(i) at least one nucleic acid sequence which binds an activator protein,
(ii) a positive selection marker gene,
(iii) DNA sequences flanking the sequences (i) and (ii) which are homologous to a nucleic acid section in the genome of the cell in order to allow a homologous recombination.

11. Eukaryotic cell, preferably a human cell obtainable by a process as claimed in ~~one of the claims 8 to 10.~~ Claims

12. Eukaryotic cell, preferably a human cell,
wherein
it contains at least one heterologous, chromosomally located, nucleic acid fragment that binds an activator protein/activator protein complex which is operatively linked with a gene that is present endogenously in the cell.

13. Process for testing the influence of non-coding nucleic acid sequences from the region of a target gene present endogenously in a eukaryotic cell on its expression which is characterized in that
(a) the cell is transfected with a vector comprising
(i) a heterologous expression control sequence that is active or can be activated in the cell which is operatively linked with a reporter gene and

(ii) non-coding nucleic acid fragments on the 5' side or/and 3' side from the region of the target gene,

(b) the cell is cultured under conditions under which the expression control sequence is active and

(c) the expression of the reporter gene is measured.

14. Process for providing a DHFR-negative eukaryotic cell, **wherein**

(a) the cell is transfected with a first vector comprising

(i) at least one target sequence for a site-specific recombinase,

(ii) DNA sequences flanking sequence (i) which are homologous to a DHFR nucleic acid sequence that is present endogenously in the cell in order to allow a homologous recombination and

(iii) optionally a positive selection marker gene and optionally a negative selection marker gene,

(b) the transfected cell is cultured under conditions under which a homologous recombination of the vector takes place and

(c) the cell obtained according to step (b) is isolated.

15. Process for introducing a heterologous DHFR gene into a eukaryotic cell,
wherein
a cell obtained by the process as claimed in claim 14

(a) is transfected with a third vector comprising

(i) optionally a positive selection marker gene which preferably differs from the positive selection marker gene of the first vector,

(ii) a nucleic acid sequence coding for a DHFR,
(iii) a nucleic acid sequence to be amplified coding for a protein in an expressible form in which each of the nucleic acid sequences from the partial sequences (i), (ii) and (iii) is flanked on the 5' side and 3' side by at least one recombinase target sequence
(b) the transfected cell is cultured under conditions under which the nucleic acid sequence flanked by recombinase target sequences is integrated into the recombinase target sequence that is already present in the genome of the cell and
(c) the cell obtained according to step (b) is isolated.

16. Vector, comprising
(i) optionally a positive selection marker gene,
(ii) a nucleic acid sequence coding for a DHFR and
(iii) a nucleic acid sequence in an expressible form coding for a desired protein

in which each nucleic acid sequence from the partial sequences (i), (ii) and (iii) is flanked on the 5' side and 3' side by at least one recombinase target sequence.

17. Vector for the homologous recombination comprising,
(i) optionally a positive selection marker gene,
(ii) at least one recombinase target sequence in each case which flanks the sequence (i),
(iii) DNA sequences flanking the sequences (i) and (ii) which are homologous to a DHFR nucleic acid sequence that is present endogenously in a cell in order to allow a homologous recombination and
(iv) optionally a negative selection marker gene outside the homologous sequences (iii).

18. Eukaryotic cell, preferably a human cell, **wherein**
(a) at least one endogenous nucleic acid sequence coding for a DHFR is inactivated and
(b) at least one recombinase target sequence is integrated into the genome in the region of this nucleic acid sequence coding for DHFR.

19. Eukaryotic cell, preferably a human cell, **characterized by**
a heterologous nucleic acid sequence in the region of an endogenous DHFR gene locus, comprising
(i) a nucleic acid sequence coding for a DHFR,
(ii) a nucleic acid sequence coding for a desired protein and
(iii) at least one recombinase target sequence.